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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/823,425	04/12/2004	Robert E. W. Hancock	UBC1110-3	4018

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EXAMINER	
ROBINSON, HOPE A	

ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 03/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/823,425	HANCOCK ET AL.	
	Examiner	Art Unit	
	Hope A. Robinson	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-41* is/are pending in the application.

4a) Of the above claim(s) *1,4-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-3* _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *4/12/04* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/8/04;12/6/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Application Status

1. Applicant's election with traverse of Group II (claims 2-3 and 39-40), in the reply filed on December 19, 2005 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Applicant's election's further election of (SEQ ID NO:6) with traverse is acknowledged. The traversal is on the grounds that the sequence should not be subjected to a restriction as there is no sequence burden. Applicant state that they strenuously object to the restriction of the sequence because SEQ ID NOS:3-12 all share extensive sequence homology and at the very least, contain conservative variations in the sequence. This argument is not persuasive as functional and structural relatedness cannot *per se* be predicted by sequence homology data only. The sequence are structurally different, thus functionally different, however, if applicant is willing to make a statement on the record that a reference that anticipates one invention would necessarily anticipate he other then the sequences will be rejoined. MPEP chapter 800 states that restriction requirement is proper if the inventions can be shown to patentably distinct and independent. Thus the restriction requirement is proper and is final.

3. Claims 1-41 are pending. Claims 2-3 are under examination. Claims 1 and 4-41 are withdrawn from further consideration pursuant to 37 CFR 1.12(b), as being drawn to a non-elected invention, there being no allowable generic or linking claim. Note that claims 39-40 do not recite "SEQ ID NO:6", thus claims 39-40 are withdrawn as directed to a non-elected subject matter.

Oath/Declaration

4. The Oath/Declaration is objected to because there are non-initialed and/or non-dated alterations made to the oath or declaration. See 37 CFR 1.52(c). See inventor Robert Hancock.

Correction is required.

Specification

5. The specification is objected to because of the following informalities:

(a) The specification is also objected to because the ATCC address disclosed on page 7 is incorrect as it is now "Manassas VA".

(b) The specification is objected to because on page 13, the priority information needs to be updated. Note that this application is a DIV of 09/143,124, which is now U.S. Patent No.6,818,407, which is a DIV of 09/143,124, now U.S. Patent No. 6,288,212.

(c) The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following is suggested: "Anti-endotoxic, Antimicrobial Cationic Peptides, the Encoding DNA and Methods of Use".

(d) The specification is objected to because the following typographical error appears throughout the instant specification, "Asieves≈" or "Apermeabilizers≈" (see page 1 for example).

(e) See also page 37 where the following appears 150 g/kg/per injection", and throughout the instant specification.

Correction is required.

Drawing

6. The drawings filed on April 12, 2004 have been accepted by the examiner.

Claim Objection

7. Claim 2 is objected to because of the following informalities:

Claim 2 is objected to because the claim depends from a non-elected claim.

Correction is required.

Information Disclosure Statement

8. The Information Disclosure Statement (IDS) filed on December 8, 2004 and December 6, 2004 has been received and entered. However, the IDS filed December 6, 2004 contains a copy of an 892 filed in a parent application which is not represented on a PTO-1449 Form. Note that the reference has been considered as it is listed on the attached 892.

Claim Rejections - 35 USC ∋ 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 2-3 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claimed invention is directed to a polynucleotide encoding a peptide said to be an antimicrobial peptide with a sequence set forth in SEQ ID NO:6 and analogs, derivatives amidated variations and conservative variations thereof (see claim 2). Claim 3 is directed to a polynucleotide encoding a peptide consisting of a specified structure,

however, no functional limitation is set forth in the claim for said peptide. The claimed invention encompasses a genus of peptides not adequately described. Additionally, the instant specification does not demonstrate possession of the analogs or derivatives or amidated variations or conservative variations thereof. The specification fails to provide any additional representative species of the claimed genus to show that applicant was in possession of the claimed genus.

A representative number of species means that the species, which are adequately described are representative of the entire genus. The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, disclosure of drawings, or by disclosure of relevant identifying characteristics, for example, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. The claimed genus of peptides could include non-functional proteins or proteins with a different function than the one described. Therefore, the genus of claimed polypeptides encompasses widely variant species.

Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir.1991), states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in *possession of the*

invention. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116). The skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. *See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993).* Therefore, for all these reasons the specification lacks adequate written description, and one of skill in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

10. Claims 2-3 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the protein set forth in SEQ ID NO:6 and the disclosure in University of British Columbia (WO 96/28559, 19 September 1996), does not reasonably provide enablement for any analog or derivative thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. The enablement requirement refers to the requirement that the specification describe how to make and how to use the invention. There are many

factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. These factors include, but are not limited to: Quantity of Experimentation Necessary; Amount of direction or guidance presented; Presence or absence of working examples; Nature of the Invention; State of the prior art and Relative skill of those in the art; Predictability or unpredictability of the art and Breadth of the claims (see *In re Wands, 858 F.2d at 737, 8 USPQ2d at1404 (Fed. Cir. 1988)*. The factors most relevant to the instant invention are discussed below.

The claimed invention encompasses an unspecified amount of derivatives, analogs, amidated variations and conservative variations for the claimed peptides. The peptides are described as being antimicrobial with respect to claim 2, however, following the modifications contemplated the encoded peptide may not be functional or have a different biological activity. In addition, the claimed polynucleotide encodes the peptide set forth in claim 3, which is not defined by a functional limitation. Undue experimentation would be required to practice the claimed invention commensurate in scope with the claims as no correlation is made between function and structure of the encoded peptide. To construct and test the unspecified amount of analogs, derivatives, amidated variations and conservative variations would require undue experimentation.

A skilled artisan would first have to construct the copious amount of analogs, derivatives, amidated variations and conservative variations absent guidance/direction as to the composition of amino acids that can be tolerated in the structure; test the peptide for belonging to the family antimicrobial peptides and further test to see if the

peptide belongs to the class antimicrobial cationic peptide (see page 5 of the specification) that have antimicrobial and anti-endotoxin activity (see page 8 of the specification). While the instant specification describes means such as site-directed mutagenesis (page 9) for constructing mutants of the claimed peptide, these methods do not enable one of skill in the art to make all, or a relevant portion of, the peptides encoded by the polynucleotide within the scope of the claims. The ability to find an analog or derivative or amidated variation encoding gene, which is structurally related to the claimed polynucleotide that encodes SEQ ID NO:6; and functionally related to antimicrobial cationic peptides having antimicrobial/anti-endotoxin activity, is not equivalent to the ability to making an antimicrobial cationic peptide encoding gene as required by the statute (i.e., "make and use"). No description in the specification or the art provides particular residues whose encoding is important within the disclosed sequence so that it's an analog or derivative etc. of an antimicrobial cationic peptide. Thus, one of skill in the art would be unable to predict the structure of the other members of the genus in order to make such members. Therefore, the instant claims are not enabled to the full extent of their scope.

Predictability of which potential changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (for example, expectedly intolerant to modification), and detailed knowledge of the ways in which the protein's structure relates to its function. In addition, one skilled in the art would expect any tolerance to

modification for a given protein to diminish with each further and additional modification, for example, multiple substitutions. In this case, the necessary guidance has not been provided in the specification. Therefore, while it is known in the art that many amino acid substitutions are possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited, as certain positions in the sequence are critical to the protein's structure/function relationship. It is also known in the art that a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many cases. For example, various sites or regions directly involved in binding activity and in providing the correct three-dimensional spatial orientation of binding and active sites can be affected (see Wells, Biochemistry, vol. 29, pages 8509-8517, 1990). The instant specification provides no guidance/direction as to which regions of the protein would be tolerant of modifications and which would not, and it provides no working examples of any variant sequence that is encompassed by the claims. It is in no way predictable that randomly selected mutations, such as deletions, substitutions, additions, etc., in the disclosed sequences would result in a protein having activity comparable to the one disclosed. As plural substitutions for example are introduced, their interactions with each other and their effects on the structure and function of the protein is unpredictable. The skilled artisan would recognize the high degree of unpredictability that all the fragments/variants encompassed in the claims would retain the recited function.

The state of the prior art provides evidence for the high degree of unpredictability as stated above. Seffernick et al. (J. Bacteriology, vol. 183, pages 2405-2410, 2001) disclose two polypeptides having 98% sequence identity and 99% sequence identity, differing at only 9 out of 475 amino acids (page 2407, right column, middle and page 2408, Fig. 3). The polypeptides of Seffernick et al. are identical along relatively long stretches of their respective sequences (page 2408, Fig. 3), however, these polypeptides exhibit distinct functions. The modifications exemplified in the Seffernick et al. reference is small compared to those contemplated and encompassed by the claimed invention.

The specification lacks adequate guidance/direction to enable a skilled artisan to practice the claimed invention commensurate in scope with the claims. Furthermore, while recombinant and mutagenesis techniques are known in the art, it is not routine in the art to screen large numbers of mutated proteins where the expectation of obtaining similar activity is unpredictable based on the instant disclosure. The amino acid sequence of a protein determines its structural and functional properties, and predictability of what mutations can be tolerated in a protein's sequence and result in certain activity, which is very complex, and well outside the realm of routine experimentation, because accurate predictions of a protein's function from mere sequence data are limited, therefore, the general knowledge and skill in the art is not sufficient, thus the specification needs to provide an enabling disclosure.

The working examples provided do not rectify the missing information in the instant specification pertaining to the claimed variants. The nature and properties of this

claim is difficult to ascertain from the examples provided as one of skill in the art would have to engage in undue experimentation to construct the variants of the claimed invention and examine the same for function.

The specification does not provide support for the broad scope of the claims, which encompass an unspecified amount of variants, analogs and derivatives. The claims broadly read on any variants, analogs and derivatives thereof for the given sequence (SEQ ID NO:6). The issue in this case is the breath of the claims in light of the predictability of the art as determined by the number of working examples, the skill level artisan and the guidance presented in the instant specification and the prior art of record. This make and test position is inconsistent with the decisions of *In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970)* where it is stated that "...scope of claims must bear a reasonable correlation to scope of enablement provided by the specification to persons of ordinary skill in the art...". Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. See *In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).* Thus, for all these reasons, the specification is not considered to be enabling for one skilled in the art to make and use the claimed invention as the amount of experimentation required is undue, due to the broad scope of the claims, the lack of guidance and working examples provided in the specification and the high degree of unpredictability as evidenced by the state of the prior art, attempting to construct and test variants of the claimed invention would constitute undue experimentation. Making

and testing the infinite number of possible variants to find one that functions as described is undue experimentation. Therefore, applicants have not provided sufficient guidance to enable one of skill in the art to make and use the claimed invention in a manner that reasonably correlates with the scope of the claims, to be considered enabling.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 2-3 are rejected under 35 U.S.C. 102(b) as being anticipated by University of British Columbia (WO 96/28559, 19 September 1996).

The University of British Columbia teach a method for the microbial production of a cationic peptide having antimicrobial activity (useful for treatment of bacterial growth and for treatment of endotoxemia-associtated disorders) and the encoding DNA (see abstract, pages 3 and 6). The reference teaches the sequence KWKLFKKIGIGAVLKVLTTGLPALKLTK (CEMA, SEQ ID NO:24) which is identical to the instant SEQ ID NO:6 and the sequence KWKLFKKIGIGAVLKVLTTGLPALIS (CEME, SEQ ID NO:23) which anticipates the claimed variant or analog or derivative

thereof for the instant SEQ ID NO:6. Therefore, the limitations of the claims are met by the reference.

Basis For Statutory Double Patenting

12. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

13. Claim 2-3 are rejected under 35 U.S.C. 101 as claiming the same invention as that of claim 2 of U.S. Patent No. 5,707,855. The claims in both applications have the same language, scope, wording and subject matter. Both applications claim an isolated polynucleotide encoding a peptide. In the instant application the peptide is contained in SEQ ID NO:6 and the patented peptide is contained in SEQ ID NO:24 (CEMA), however, both sequence has the same structure, KWKLFKKIGIGAVLKVLTTGLPALKLTK. This is a double patenting rejection.

Conclusion

14. No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hope A. Robinson whose telephone number is 571-272-0957. The examiner can normally be reached on Monday-Friday.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr, can be reached at (571) 272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Hope Robinson, MS 3/4/06

Patent Examiner

HOPE ROBINSON
PATENT EXAMINER